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Tobert

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(54) **COMBINATION THERAPY FOR REDUCING THE RISKS ASSOCIATED WITH CARDIOVASCULAR DISEASE**

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(51) **Int. Cl.⁷** **A61K 31/35**; A61K 31/505

(52) **U.S. Cl.** **514/455**; 514/260

(58) **Field of Search** 514/455, 260

(56) **References Cited**

U.S. PATENT DOCUMENTS

- | | | |
|---------------|---------|----------------------------|
| 3,895,107 A | 7/1975 | Morrison |
| 5,084,482 A | 1/1992 | Hirsch et al. |
| 5,470,845 A * | 11/1995 | Magrin et al. 514/121 |
| 5,631,401 A | 5/1997 | Stein et al. |

FOREIGN PATENT DOCUMENTS

- | | | |
|----|---------------|---------|
| DE | 232 580 9 | 12/1974 |
| DE | 235 729 9 | 5/1975 |
| DE | 43 26 698 | 3/1995 |
| WO | 43 26 698 A 1 | 3/1995 |

OTHER PUBLICATIONS

Hopkins et al.; "Folic acid may protect patients with early heart disease"; American Heart Association News Release No. NR 95-4320, Sep. 11, 1995.*

Dobs, A. et al., "Lipid-lowering Diets in patients taking pravastatin, a new HMG-CoA reductase inhibitor: compliance and adequacy", American Journal of Clinical Nutrition, vol 54, No. 4, pp. 696-700, 1991.

Frohlich, et al., "Lipoproteins and homocyst(e)ine as risk factors for atherosclerosis: Assessment and treatment", Canadian Journal of Cardiology, vol. 11, pp. 18C-23C, 1995.

The Merck Manual of Diagnosis and Therapy, 16th Edition, pp. 1044-1045, 1992.

Boushey, et al., "A Quantitative Assessment of Plasma Homocysteine as a Risk Factor For Vascular Disease", JAMA, vol. 274, No. 13, pp. 1049-1057, 1995.

Mayer, et al., "Homocysteine and Coronary Atherosclerosis", Journal of The American College of Cardiology, vol. 27, No. 3, pp. 517-527, 1996.

Feher, et al., "Long-term safety of statin-fibrate combination treatment in the management of hypercholesterolaemia in patients with coronary artery disease", British Heart Journal, British Medical Association, vol. 74, No. 1, pp. 14-17, 1995.

Tonstad, et al., "Low dose colestipol in adolescents with familial hypercholesterolaemia", Archives of Disease in Childhood, vol. 74, No. 2, pp. 157-160, 1996.

Hopkins et al., "Folic acid may protect patients with early heart disease"; American Heart Association News Release No. NR 95-4320 (Sep. 11, 1995).

Ubbink et al., "Vitamin Requirements for the Treatment of Hyperhomocysteinemia in Humans", J. Nutr., vol. 124 (10), pp. 1927-1933 (Oct. 1994).

Robinson et al., "Homocysteine and coronary artery disease", Cleve. Clin. J. Med., vol. 61 (6), pp. 438-450 (Nov.-Dec. 1994).

M. Rene Malinow, "Plasma Homocysteine and arterial occlusive disease: a mini review", Clin Chem., vol. 41(1), pp. 173-176 (Jan. 1995).

Van Den Berg et al., "Hyperhomocysteinaemia and endothelial dysfunction in young patients . . .", Eur. J. Clin. Invest., vol 25, pp. 176-181 (1995).

Brattstrom et al., "Homocysteine and cysteine: determinants of plasma levels in middle aged and elderly subjects", J. Intern. Med., vol. 236(6), pp. 633-641 (1994).

Stampfer et al., "Can lowering homocysteine levels reduce cardiovascular risk?", N. Eng. J. of Med., vol. 332(5), pp. 328-329 (Feb. 1995).

Dudman et al., "Disordered methionine/homocysteine metabolism in premature vascular disease", Arteriosclerosis and Thrombosis, vol. 13(9), pp. 1253-1260 (Sep. 1993). Glueck et al., "Evidence that homocysteine is an independent risk factor for atherosclerosis in hyperlipidemic patients", Amer. J. Cardiology, vol. 75(2), pp. 132-136 (Jan. 1995).

Dalery et al., "Homocysteine and coronary artery disease in French Canadian subjects . . .", Amer. J. Cardiology, vol. 75(16), pp. 1107-1111 (Jun. 1995).

Pancharuniti et al., "Plasma homocysteine, folate and vitamin B-12 concentrations and risk for early onset coronary artery disease", Amer. J. Clin. Nutr., vol. 59(4), pp. 940-948 (Apr. 1994).

Ubbink et al., "Vitamin B-12, vitamin B-6 and folate nutritional status in men with hyperhomocysteinemias", Amer. J. Clin. Nutr., vol. 57(1), pp. 47-53 (Jan. 1993).

(List continued on next page.)

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(57)

ABSTRACT

The instant invention provides methods for preventing or reducing the risk of developing atherosclerosis, as well as for halting or slowing the progression of atherosclerotic disease once it has become clinically evident, comprising the administration of a therapeutically effective amount of an HMG-CoA RI in combination with folic acid or a pharmaceutically acceptable salt or ester thereof to a person who is at risk of developing atherosclerosis or who already has atherosclerotic disease.